REMARKS

The presently claimed invention features fohy030 and fomy030 polypeptides. Fohy030 and fomy030 are expressed at a much lower level melanoma cells having relatively high metastatic potential than in melanoma cells having relatively low metastatic potential. Accordingly, fohy030 and fomy030 polypeptides and nucleic acids are useful in the diagnosis and monitoring of melanoma.

Claims 43 and 51-56 have been amended to specify that the presence of the claimed polypeptide "in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide." Support for this amendment is found in the specification, for example, at pages 123-127, particularly on page 127 at lines 5-24.

Rejections Under 35 U.S.C. §101

The Examiner rejected claims 29, 31-38, 43 and 45-56 under 35 U.S.C. §101 as allegedly lacking utility. Applicant traverses the rejection of claims 29, 31-38, 43 and 45-56.

According to the Examiner, claims 29, 31-38, 43 and 45-56 lack utility because "one of skill in the art would not be able to predict if SEQ ID NO:2, 6 and 8 were in fact translated into the polypeptides of SEQ ID NO:3, 7 and 9." In support of this assertion, the Examiner cited a number of publications said to describe genes that are subject to control at the translational level (McClean et al.; Alberts et al.; Shantz et al.; and Fu et al.)

The cited publications do not support the Examiner's assertion that it cannot be predicted that "SEQ ID NO:2, 6 and 8 were in fact translated into the polypeptides of SEQ ID NO:3, 7 and 9." This is because all of the genes studied in the cited publications produce an mRNA that is translated into polypeptide. Thus, the publications cited by the Examiner do not provide a reasonable basis for doubting that fohy030 mRNA is translated into polypeptide.

As an initial matter, not all of the publications cited by the Examiner describe a gene that is subject to regulation at the level of translation. McClean et al. does not appear to suggest that the Pgp gene is regulated at the level of translation. Rather, McClean et al. discloses that, under some circumstances, the half-life of Pgp protein is increased such that Pgp mRNA levels are not directly proportional to Pgp protein levels. Thus, McClean et al. does not support the

Examiner's assertion that it cannot be predicted whether a given mRNA will be translated into polypeptide. Indeed, far from suggesting that it is unpredicatable whether an mRNA will produce polypeptide, McClean et al. suggests that an mRNA can produce more polypeptide than one might otherwise predict.

Alberts et al., Shantz et al. and Fu et al. do appear to describe examples of translational regulation. However, these examples of translational regulation are simply inadequate to support the Examiner's assertion regarding the fohy030 gene and the fomy030 gene for at least two independent reasons. First, all of the genes studied in the cited publications do produce polypeptide under at least some circumstances. Thus, the publications do not provide any basis for asserting that a given mRNA might not be translated into polypeptide. Second, the genes described in the publications as being subject to translational regulation include specialized regulatory elements. The Examiner has not provided any evidence that such regulatory elements are present in the fohy030 gene and the fomy030 gene.

The cited publications do not support the assertion that it is unpredictable whether a given mRNA is translated into polypeptide

First, every single gene studied in Alberts et al., Shantz et al., and Fu et al. produces a polypeptide under at least some circumstances. Indeed, for at least one gene the amount of protein produced under certain conditions is greater than might be assumed based on the amount mRNA produced. For example, Shantz et al. state that "[i]n virtually all of the circumstances reported in which enhanced levels of AdoMetDC mRNA have been observed, the increases in mRNA are insufficient to account for the increases in AdoMetDC protein content". Even the p53 gene, which sometimes does not produce detectable protein despite the presence of measurable mRNA, produces measurable protein in many situations (see Fu et al. at p. 4393). Because every gene studied in the publications cited by the Examiner produces mRNA and also produces polypeptide, the publications do not support the Examiner's assertion that it is unpredictable whether fohy030 and fomy030 mRNA are translated into polypeptide.

The cited publications do not provide any basis for concluding that the fohy030 gene and the fomy030 gene are subject to translational control

Second, the genes described in each of the publications cited by the Examiner include specific structural elements or other factors that appear to be required for translational control. For example, the ferritin mRNA produced by the ferritin gene described in Alberts et al. includes a 3' stem loop structure to which an iron-responsive regulatory protein binds in order to regulate translation. Shantz et al. identify at least three structural features of ODC mRNA that are likely to be responsible for translational regulation: 5' UTR in the mRNA that can adopt a specific secondary structure that might be melted by certain translation factors, an internal ORF, and a potential polyamine responsive element in the 5' UTR. Shantz et al. report that translational regulation of the AdoMetDC gene might be due to a small ORF in the 5'UTR of the mRNA and a polyamine response element in the 5' UTR of the mRNA. Fu et al. report that translational control of p53 observed in some cell types may be due to the presence of a specific sequence in the 3' UTR of the mRNA. Thus, each gene studied in the cited publications includes special structural elements are responsible for the observed translational regulation. The Examiner has not provided any evidence suggesting that any of these specialized elements are present in the fohy030 and fomy030 genes. Thus, there is no reason to conclude that the fohy030 and fomy030 genes include any of the elements that lead to translational control or that the fohy030 and fomy030 genes are subject to translational control.

The expression pattern of fohy030 mRNA suggests that it is translated into polypeptide

As the specification explains, the expression of fohy030 in clinical samples of melanoma cells is inversely correlated with metastatic potential. This suggests that transcription of the fohy030 gene is under some type of control. From a biological perspective it seem illogical to suggest that a gene whose transcription is controlled is not translated into a polypeptide. It is difficult to imagine the biological rationale for controlling transcription of a gene whose polypeptide is never expressed. It seems far more reasonable to assume that transcription of a

gene differs from one cell type to another because the polypeptide produced by the gene has a impact on the cells in which it is expressed.

The Examiner has provided no basis for concluding that it cannot be predicted that fohy030 mRNA and fomy030 mRNA are translated into polypeptide and has not meet the initial burden of challenging Applicants assertion of utility

Given that all of the genes in the publications cited by the examiner do produce polypeptide despite the presence of translational control and given the fact that there is no evidence that the structural elements required for the various types of translational control described in the publications cited by the Examiner are present in the fohy030 gene, the publications simply do not support the Examiner's assertion that one could not predict that fohy030 polypeptide is produced. Even if the fohy030 gene were subject to translational control, it would not be mean that it could not be predicted that fohy030 mRNA produces polypeptide. Indeed, the very idea of translation control means that the mRNA is translated into polypeptide. There could hardly be translation control without translation.

Given that the Examiner has not provided any reasonable basis for concluding that it could not be predicted that "SEQ ID NO:2, 6 and 8 [are] in fact translated into the polypeptides of SEQ ID NO:3, 7 and 9," the rejection under 35 U.S.C. §101 is improper. "The PTO has the initial burden of challenging a patent applicant's presumptively correct assertion of utility. ...If the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility, however, the burden shifts to the applicant to submit evidence sufficient to convince such a person of the invention's asserted utility." *In re Swartz*, 232 F.3d 862, 866 (Fed. Cir. 2000). The Examiner has not met his burden of providing evidence or reasoning that would cause one of ordinary skill to doubt the utility of the presently claimed invention.

Moreover, even if the fohy030 gene were subject to some degree of translational control in certain circumstances, Applicants fail to understand why the presence of translational control would lead the Examiner to conclude that claims 29 and 31-38 lack utility. The claimed polypeptides retain their utility for producing anti-fohy030 antibodies and other purposes irrespective of whether the fohy030 gene is subjected to translational control.

In view of the forgoing, Applicants respectfully request that the rejection of claims 29 and 31-38 under 35 U.S.C. §101 be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected claims 29, 31-38 and 45-56 under 35 U.S.C. §112, first paragraph as allegedly not enabled. The Examiner stated that this rejections was based, in part, on the rejection of these claims for lack of utility under 35 U.S.C. §101. The Examiner also stated that even if the Applicant overcame the lack of utility rejection under 35 U.S.C. §101, claims 43 and 45-56 as well as claims 37 and 38 would still be rejected as allegedly not enabled. Applicant addressed the rejections under 35 U.S.C. §101 above. With respect to the rejections under the enablement requirement of 35 U.S.C. §112 that are not linked to a rejection under 35 U.S.C. §101, it is Applicant's position that the specification teaches one of ordinary skill in the art how to make and how to use the claimed invention.

Claims 43 and 45-56

Amended claims 43 and 45-56 are drawn to polypeptides that are encoded by a nucleic acid molecule that hybridizes under defined conditions to a nucleic acid molecule consisting of the nucleotide sequence of a specified fohy030 or fomy030 cDNA and which when expressed in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide. Such polypeptides are enabled because one skilled in the art can readily identify nucleic acid molecules which hybridize under the specified conditions to the defined nucleic acid molecules. For example, as the specification explains, the fohy030 cDNA was identified by screening a human retina cDNA library using the fomy030 cDNA as a probe (see pages 119-120 of the specification). One can then test whether expression of the polypeptide encoded by the hybridizing nucleic acid molecule in a melanoma cells results in decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide. For example, the specification describes experiments in which both the metastatic potential and fohy030 expression of melanoma cells were measured. Similar techniques can be

applied to cells that naturally expressed or have been genetically modified to express the claimed polypeptide.

Claims 37 and 38

The Examiner argued that claims 37 and 38 are not enabled because "the specification does not suggest a function associated with an isolated fragment of SEQ ID NO:7 consisting of residues 1-844 or residues 850-1497 of SEQ ID NO:7 or a protein comprising one of amino acid residues 1-844 or residues 850-1497 of SEQ ID NO:7." It is Applicant's position that the claimed polypeptides are enabled irrespective of whether they retain the function of the full-length naturally-occurring polypeptide. For example, such polypeptides are useful for generating antibodies that can be used to assess fohy030 expression for diagnostic purposes. The preparation of the claimed polypeptides and their use in the generation of antibodies is well within abilities of one of ordinary skill in the art.

The Examiner also argued that claims 37 and 38 are not enabled because the "specification does not teach that amino residues 1-844 and 850-1497 of SEQ ID NO:7 would retain activity when inserted separately into different proteins." As discussed above, the claimed polypeptides are useful whether or not they retain the function of the full-length naturally-occurring polypeptide. In addition, the presence of flanking amino acid sequences does not render the portions of SEQ ID NO:7 useless for antibody generation. Fusion proteins are commonly used for the generation of antibodies as the overall size of the immunogen is believed to influence immunogenicity.

Rejections Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected claims 37, 38, 43 and 45-56 under 35 U.S.C. §112, first paragraph as allegedly not supported by an adequate written description.

The Examiner stated that Applicant's earlier submitted arguments for regarding the adequacy of the written description supporting claims 37, 38 and 45-56 was not persuasive because "the specification did not provide any objective evidence that applicant had the variant polypeptide in hand at the time the instant application was filed." Applicants request that the Examiner clarify the requirement that the specification provide "objection evidence" that

"applicant had the variant polypeptide in hand." The Examiner's reference to "objective evidence" suggests that the Examiner is requiring evidence that Applicant had actually reduced the claimed polypeptides to practice at the time the application was filed and thus had actual physical possession of the claimed polypeptides. Applicants do not believe that the relevant case law imposes such are requirement. As explained in greater detail below, The specification provides an adequate written description of the claimed polypeptides by virtue of providing a description of their structure and or physical properties.

Claims 37 and 38

In rejecting claims 37 and 38 the Examiner emphasized that the *Lilly* court held that "a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus." However, the present claims differ from those in *Lilly* in the genus of nucleic acid in claims 37 and 38 is not defined by function.

Regents of the University of California v. Lilly & Co., 119 F.3d 1559, 1563 (Fed. Cir. 1997), emphasizes that an appropriate written description of a cDNA "requires a precise definition, such as by structure, formula, chemical name, or physical characteristics." *Lilly* holds that a proper written description of a genus of cDNAs can be achieved in two alternative ways: "by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within in the scope of the genus **or** of a recitation of structural features common to members of the genus." *Lilly*, 119 F.3d at 1563 (emphasis added). However, assuming the same standard applies to polypeptides, an assumption that the Examiner clearly has made, there are two different ways to provide an adequate written description of a genus of polypeptides. One way is to provide structural features common to members of the genus. Claims 37 and 38 are drawn to polypeptides comprising specified amino acid sequences. To the extent that such claims are genus claims, the specified sequence amounts to a description of a structural feature (i.e., a substantial portion of SEQ ID NO:7) common to members of the genus.

Claims 43 and 45-56

Claims 43 and 45-56 are drawn to drawn to polypeptides that are encoded by a nucleic acid molecule that hybridizes under defined conditions to a nucleic acid molecule consisting of the nucleotide sequence of a specified fohy030 or fomy030 cDNA and which when expressed in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide. Thus, the polypeptides are defined via the nucleic acid molecules encoding them. This amounts to a structural definition based on the sequence of the polypeptide, which sequence is defined by the sequence of the hybridizing nucleic acid molecule that encode the polypeptide. Thus, it is Applicant's position that the written description requirement has been fully met for claims 43 and 45-56.

In view of the forgoing, Applicants respectfully request that the rejection of claims 27, 28 and 45-56 under the written description requirement of 35 U.S.C. §112, first paragraph be withdrawn.

Conclusion

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 17 OCT 2001

Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

Version with markings to show changes made

In the claims:

Claims 43 and 51-56 have been amended as follows:

43. An isolated polypeptide selected from the group consisting of:

a) a polypeptide consisting of 542 amino acids and encoded by a nucleic acid molecule that hybridizes to the nucleic acid molecule of SEQ ID NO:2 or its complement at 68°C in 0.1X SSC, 0.1% SDS;

b) a polypeptide consisting of 1497 amino acids and encoded by a nucleic acid molecule that hybridizes to the nucleic acid molecule of SEQ ID NO:6 or its complement at 68°C in 0.1X SSC, 0.1% SDS;

c) a polypeptide consisting of 1533 amino acids and encoded by a nucleic acid molecule that hybridizes to the nucleic acid molecule of SEQ ID NO:8 or its complement at 68°C in 0.1X SSC, 0.1% SDS;

d) a polypeptide consisting of 542 amino acids and encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule having the sequence of the cDNA of the clone contained in NRRL Deposit No. B-21426 at 68°C in 0.1X SSC, 0.1% SDS;

e) a polypeptide consisting of 1497 amino acids and encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule having the sequence of the cDNA of the clone contained in ATCC Accession No. 97880 at 68°C in 0.1X SSC, 0.1% SDS; and

f) a polypeptide consisting of 1533 amino acids and encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule having the sequence of the cDNA of the clone contained in ATCC Accession No. 97881 at 68°C in 0.1X SSC, 0.1% SDS,

wherein the presence of the polypeptide in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide.

51. An isolated polypeptide encoded by a nucleic acid molecule that comprises at least 30 nucleotides and hybridizes to the nucleic acid molecule of SEQ ID NO:2 or its complement at 68°C in 0.1X SSC, 0.1% SDS, wherein the presence of the polypeptide in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide.

52. An isolated polypeptide encoded by an nucleic acid molecule that comprises at least 30 nucleotides and hybridizes to the nucleic acid molecule of SEQ ID NO:6 or its complement at 68°C in 0.1X SSC, 0.1% SDS, wherein the presence of the polypeptide in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide.

53. An isolated polypeptide encoded by a nucleic acid molecule that comprises at least 30 nucleotides and hybridizes to the nucleic acid molecule of SEQ ID NO:8 or its complement at 68°C in 0.1X SSC, 0.1% SDS, wherein the presence of the polypeptide in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide.

54. An isolated polypeptide encoded by a nucleic acid molecule that comprises at least 30 nucleotides and hybridizes to a nucleic acid molecule having the sequence of the cDNA of the clone contained in NRRL Deposit No. B-21416 at 68°C in 0.1X SSC, 0.1% SDS, wherein the presence of the polypeptide in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide.

55. An isolated polypeptide encoded by a nucleic acid molecule that comprises at least 30 nucleotides and hybridizes to a nucleic acid molecule having the

sequence of the cDNA of the clone contained in ATCC Accession No. 97880 at 68°C in 0.1X SSC, 0.1% SDS, wherein the presence of the polypeptide in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide.

56. An isolated polypeptide encoded by a nucleic acid molecule that comprises at least 30 nucleotides and hybridizes to a nucleic acid molecule having the sequence of the cDNA of the clone contained in ATCC Accession No. 97881 at 68°C in 0.1X SSC, 0.1% SDS, wherein the presence of the polypeptide in a melanoma cell is associated with decreased metastatic potential of the melanoma cell compared to an otherwise identical melanoma cell that does not express the polypeptide.